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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,878	09/15/2006	Siegfried Ansorge	P29679	2223

7055 7590 03/21/2011

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EXAMINER	
COPPINS, JANET L	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
03/21/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/575,878	ANSORGE ET AL.	
	Examiner	Art Unit	
	JANET L. COPPINS	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *138-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *138 and 139* is/are allowed.

6)☒ Claim(s) *140,141 and 143* is/are rejected.

7)☒ Claim(s) *142 and 144* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 138-145 are now pending in the instant application.

Response to Amendment

2. Applicants' Amendment of January 6, 2011, has been reviewed by the Examiner and entered of record in the file. Accordingly, pending claims 118-137 have been cancelled and new claims 138-145 have been added.

Previous Claim Rejections - 35 USC § 112

3. Claims 118-126 previously rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 118 rejected for reciting the limitation "X1, X2, X3, and X4 represent identical or different carbon units," which is unclear because the limitation "carbon units" is not defined in the specification. Claim 118 also recites the limitation, "R1 and R2 symbolize a substitution pattern of a respective partial ring," in which the terms " substitution pattern" and "respective partial ring" are unclear because they are not defined in the specification.

Claims 124-126 recite the limitation, "wherein the substituents R1 represent hydrogen." Since R1 represents from one to four substituents, it is unclear if these limitations mean that a) all substituents R1 are identical and all hydrogen or that b) one of substituents R1 can be hydrogen at any given time.

Applicants have cancelled said claims, therefore the 35 U.S.C. 112, second paragraph, rejections have been rendered moot and are withdrawn.

Previous Claim Rejections - 35 USC § 102

4. Claims 118-126 previously rejected under 35 U.S.C. 102(b) as being anticipated by Pamukcu et al. (U.S. Patent no. 6,410,584). Since claims 118-126 have been cancelled, the anticipation rejections have been rendered moot and are withdrawn.

New Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 140, 141 and 143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification, while being enabling for methods for treating diseases such as asthma, inflammation, COPD, certain dermatological conditions, etc., does not reasonably provide enablement for the "laundry list" of diseases recited in claim 140, or for the **prevention** of said diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Claim 140 recites, "A method of preventing or treating at least one condition selected from …["laundry list" of dozens of diseases and conditions] comprising administering to the subject the composition of claim 138 in an amount sufficient for preventing or treating the at least one condition."

The nature of the invention in claims 140, 141 and 143 is a method for the treatment or prevention of diseases involving the dipeptidyl peptidase IV and aminopeptidase enzymes.

The Breadth of the Claims

The applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." MPEP §2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Applying this rule to **Claim 140**, the scope of the diseases recited is reasonably interpreted as an open-ended number of diseases, as neither the Specification or claims provides a closed set of diseases or conditions which sets boundaries on the limitations of, for example, "other autoimmune diseases; inflammatory diseases; other allergic diseases; skin and mucosa diseases; acute neuronal diseases; chronic neuronal diseases; prion-caused diseases; other tumors as well as metastases; and sepsis-like conditions."

Considering the differences in etiology and patient populations between, say, "dermatological diseases," "COPD," and "multiple sclerosis," the scope of illnesses covered by **Claim 140** encompass a very broad spectrum of human morbidity.

The state of the prior art

The diseases that the instant claims allege for treating include inflammatory,

neurodegenerative and autoimmune diseases, etc., as well as cancer. The state of the art at the time of this application was that methods for treating Alzheimer's disease, prion-mediated diseases, multiple sclerosis, etc. were not well-established in the art.

As an example, at the time of this application, there were only four medications approved in the United States for the treatment of mild-to-moderate **Alzheimer's disease** (tacrine, donepezil, rivastigmine, and galantamine), and one medication for moderate-to-severe Alzheimer's disease (memantine). For example, even though it was known at the time of the application that the β-amyloid (Aβ) peptide production pathway was involved in the pathology of Alzheimer's disease, it had not been clearly demonstrated in the art that agents which were shown to inhibit β-amyloid production in vitro, were enabled for the treatment of the disease. Although the clinical and neuropathological aspects of neurodegenerative diseases are distinct, their unifying feature is that each disease has a characteristic pattern of neuronal degeneration in anatomically or functionally related regions. Presently available pharmacological treatments for the neurodegenerative disorders are symptomatic and do not alter the course of or progression of the underlying disease (see Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 10^{th} Edition, page, 549). Even if the patient has a genetic predisposition to the selected identified disease states, one is still treating the individual patient, and not preventing. It has not been shown in the specification that the prophylaxis of such disease is accepted in the art as being predictive of the utility alleged, especially when absent of pharmacological data.

Similarly, at the time of this application, although there had been substantial progress reported in the scientific literature about the multiple etiologies of autoimmune diseases such as

multiple sclerosis, including genetic makeup and environmental factors, multiple sclerosis remains a difficult disease for which solutions seem attainable yet remain elusive.

The level of skill in the art

Practitioners in this art (medical clinicians, pharmacists and/or pharmaceutical chemists) would presumably be highly skilled in the art for treatment of persons with the claimed diseases. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The predictability or lack thereof in the art

Because of high level of unpredictability associated with the treatment, let alone "prevention," of certain diseases such as dementia, Multiple Sclerosis, or cancer, a greater amount of evidentiary support is needed to fully satisfy the requirement of 35 U.S.C 112, first paragraph. A survey of scientific literature indicates that the etiologies or mechanisms of those diseases or conditions known to involve aminopeptidase or dipeptidyl peptidase production, such as Alzheimer's disease and Multiple Sclerosis, were not completely understood or settled at the time of the application. As a result, the art had few benchmarks by which to measure the effectiveness of inhibitors of aminopeptidase or DPPIV inhibitors in treating such diseases. The art therefore remains highly unpredictable, particularly as to methods of prevention, using compounds which were studied only for their inhibitory activity in in vitro assays or in murine models.

As an example, methods for treating **Alzheimer's disease** were highly unpredictable at the time of this application. There are presently only four medications approved in the United States for the treatment of mild-to-moderate Alzheimer's disease (tacrine, donepezil, rivastigmine, and galantamine), and one medication for moderate-to-severe Alzheimer's disease (memantine). However, there do not appear to have been any reported clinical studies at the time of this application showing that chemical compounds which demonstrate "dipeptidyl peptidase inhibitory activity" in in vitro assays were effective in "treating" Alzheimer's disease.

In re Fisher, 427 F.2d 833, 839; 166 USPQ 18, 24 (CCPA 1970) held that, "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." In other words, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute.

The nature of the pharmaceutical arts is such that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability, even in view of the high level of skill in the art. This unpredictability is more pronounced where the diseases and conditions disclosed in the Specification are as complex and diverse as autoimmune diseases such as multiple sclerosis; and neuronal diseases such as dementia, Huntington's, Parkinson's, and Alzheimer's disease, as claimed in this application.

It is noted that pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary

in order to satisfy the statue. The nature of pharmaceutical arts is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present and

The presence or absence of working examples

The present application does provide in vitro data showing inhibition of alanyl aminopeptidase and dipeptidyl peptidase IV activity, by selected compounds of the present invention. (See Specification at pages 24- 51, Examples 1-4). Specifically, the application discloses experimental data that the instant compounds are effective for inhibiting levels of alanyl aminopeptidase and dipeptidyl peptidase in mice. However, the claims recite methods of treating diseases such as neurodegenerative disorders and intellectual impairment disorders, using the compounds described in the specification. The compounds disclosed in the specification, which have data regarding the claimed compounds' affinitv of the dipeptidyl peptidase IV and alanyl aminopeptidase enzymes, have no pharmacological data regarding the treatment or prevention of said diseases. The specification is short of any working data (animal models or in vivo testing) in regards to the prevention of said diseases. Merely stating that the instant compounds are preventable against, for example manic depression, does not establish usefulness of the invention absent art-recognized correlation between such tests and the ultimate use.

A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that compounds fall within the scope of a claim will posses the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724. The instant specification at most only provides processes of preparation. In the absence of such information, a person of ordinary skill in the art would reasonably require an undue quantity of experimentation even to select which patients with which specific diseases or conditions could benefit (i.e., would be "treated"), from which composition of Formula (I) would be useful to treat diseases as diverse and complex as Alzheimer's disease, Parkinson's, multiple sclerosis, a prion-caused disease, and any type of cancer or cancerous tumor.

The quantity of experimentation needed

A person of skill in the art would require an undue quantity of experimentation even to select which of the broad array of diseases and conditions claimed in **Claim 140** could be treated [see "Breadth of Claims" section], given the complexity and diversity of the claimed diseases such as Alzheimer's disease, "prion-caused diseases" in humans and mammals, multiple sclerosis, etc., as well as the lack of established benchmarks in the art known at the time of this application where such diseases were treated by pharmaceutical compositions. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 , states that, "a patent is not a hunting license. It is not a reward for research, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above,

to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test if the claimed composition could treat the vast array of claimed disorders and diseases, and further, prevent said diseases, by the method encompassed in the instant claims, with no assurance of success.

It is suggested to delete the term "preventing" in claims 140, 141 and 143 to overcome the rejection, as well as limiting the scope of claim 140 to include only such diseases for which Applicants can provide enabling support in the Disclosure, i.e. bases on the experimental data provided and the in vivo murine models of Examples 1-4, the Examiner recommends limiting the diseases to inflammation, certain dermatological diseases, certain allergic disorders, asthma and COPD, and colitis, for example.

Claim Objections

7. Claims 142 and 144 are objected to as being dependent on rejected base claims.

Conclusion

8. In conclusion, claims 138-145 are currently pending, and claims 140, 141 and 143 are rejected. Claims 142 and 144 are objected to, and claims 138 and 139 appear allowable over the art of record.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. COPPINS whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571.272.8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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